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"*A STUDY OF RELATION OF HEMOGLOBIN A1C TO LEFT VENTRICULAR DIASTOLIC FUNCTION IN PATIENTS WITH TYPE 1 DIABETES MELLITUS AND WITHOUT OVERT HEART DISEASE* "

THE TAMILNADU DR MGR MEDICAL UNIVERSITIY,

CHENNAI

Certificate

*This is to certify that the dissertation entitled "**A STUDY OF RELATION OF HEMOGLOBIN A1C TO LEFT VENTRICULAR DIASTOLIC FUNCTION IN PATIENTS WITH TYPE 1 DIABETES MELLITUS AND WITHOUT OVERT HEART DISEASE** " is the bonafide original work of Dr. M.RADHA in partial fulfillment of the requirements for M.D General Medicine (Branch-I) examination of The Tamil Nadu Dr. M.G.R Medical university to be held in March 2010*

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Declaration

I ***Dr M. Radha*** *, solemnly declare that dissertation titled, "****A STUDY OF RELATION OF HEMOGLOBIN A1C TO LEFT VENTRICULAR DIASTOLIC FUNCTION IN PATIENTS WITH TYPE 1 DIABETES MELLITUS***

AND WITHOUT OVERT HEART DISEASE" *is a bonafide work done by me at Annal Gandhi Memorial hospital affiliated to K.A.P.V. Government medical college,Trichy-1,during 2007-2009 under the guidance and supervision of Prof Dr. S .PANNEER SELVAM M.D, HOD/PROF of medicine and unit chief, Prof Dr. G. ANITHA.M.D*

The dissertation is submitted to The Tamilnadu Dr.M.G.R.Medical University, towards the partial fulfillment of requirement for the award of M.D degree (Branch-I) in general medicine.

Place : Trichirappalli

Date : *Dr.M.Radha*

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CONTENTS

INTRODUCTION

INTRODUCTION

Diabetes mellitus is a syndrome of chronic hyperglycaemia due to relative insulin deficiency, resistance, or both.

It affects more than 120 million people world-wide, and it is estimated that it will affect 220 million by the year 2020.

Diabetes is usually irreversible and, although patients can have a reasonably normal lifestyle, its late complications result in reduced life expectancy and major health costs.

These include macro vascular disease, leading to an increased prevalence of coronary artery disease, peripheral vascular disease and stroke, and micro vascular damage causing diabetic retinopathy and nephropathy.

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, >360 million individuals will have diabetes by the year 2030.

Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialised.

Approximately 1.5 million individuals (>20 years) were newly diagnosed with diabetes in 2005. DM increases with ageing.

In 2005, the prevalence of DM in the United Sates was estimated to be 0.22% in those <20 years and 9.6% in those >20 years. In individuals >60 years, the prevalence of DM was 20.9%.

Type 1 diabetes is a disease resulting in insulin deficiency. In western countries almost all patients have the immune-mediated form of the disease (type 1A). Type 1 diabetes is prominent as a disease of childhood, reaching a peak incidence around the time of puberty, but can present at any age.

The Diabetes Control and Complications Trial (DCCT)[1] provided definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of type 1 DM.

In DCCT[1] trial individuals in the intensive diabetes management group achieved a substantially lower hemoglobin A1C (7.3%) than individuals in the conventional diabetes management group (9.1%).

The DCCT[1] demonstrated that improvement of glycaemic control reduced non proliferative and proliferative retinopathy (47% reduction), microalbuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycaemic control also slowed the progression of early diabetic complications.

CARDIOVASCULAR MORBIDITY AND MORTALITY

Cardiovascular disease is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in PAD, CHF, CAD, MI, and sudden death (risk increase from one- to fivefold) in DM.

The increase in cardiovascular morbidity and mortality appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors.

In the DCCT[1], the number of cardiovascular events in patients with type 1 diabetes did not differ between the standard and intensively treated groups during the trial but were reduced at follow-up 17 years later.

EFFECTS OF DIABETES ON THE MYOCARDIUM

Both systolic and diastolic abnormalities have been demonstrated in patients with Diabetes without symptomatic evidence of cardiovascular disease. These abnormalities correlate with glycaemic control, duration of diabetes and evidence of retinopathy/neuropathy (Annonu et.al 2001[21]).

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES OF THE STUDY

- To study about the echo cardio graphic findings in type -1 diabetic patients who are on regular treatment.
- To study about glycaemic control .
- To detect early cardiac changes and prevent complications.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Diabetes Mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetics and environmental factors.

History is as old as mankind. It divides into pre insulin era post insulin era. The word Diabetes in Greek means – “I run through Siphon”. The Indian name for Diabetes is Madhumeha – Honey in rain. In 16th century, Susrutha in the Sanskirit book of surgery, and Charaka in the Sanskirit book of medicine have mentioned about Diabetes. The first person -Vaidys – tested the urine of diabetic patients.

Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.

The metabolic dysregulation associated with DM causes secondary patho physiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system.

Insulin is the key hormone involved in the storage and controlled release within the body of the chemical energy available from food. It is coded for on chromosome 11 and synthesized in the beta-cells of the pancreatic islets. . After secretion, insulin enters the portal circulation and is carried to the liver.

Blood glucose levels are closely regulated in health and rarely stray outside the range of 3.5-8.0 mmol/L (63-144 mg/dL), despite the varying demands of food, fasting and exercise.

CRITERIA FOR DIAGNOSING DIABETES MELLITUS

- Symptoms of Diabetes plus random blood glucose concentration - >11.1 mmol(200 mg/dl) or
- Fasting plasma glucose- 7.0 mmol/L(126 mg/dl) or

- Two hour plasma glucose -11.1 mmol /L(200 mg/dl) during an oral glucose tolerance test

(Adapted from the American Diabetes Association, 2007.)

Fasting is defined as no caloric intake for at least 8 h.

The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.

Random is defined as without regard to time since the last meal.

Etiologic Classification of Diabetes Mellitus

I. **Type 1 diabetes** (cell destruction, usually leading to absolute insulin deficiency)

A. Immune-mediated

B. Idiopathic

II. **Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. **Other specific types of diabetes**

A. **Genetic defects of cell function** characterized by mutations in:

1. Hepatocyte nuclear transcription factor (HNF) 4 (MODY 1)
2. Glucokinase (MODY 2)
3. HNF-1 (MODY 3)
4. Insulin promoter factor-1 (IPF-1; MODY 4)
5. HNF-1 (MODY 5)
6. NeuroD1 (MODY 6)
7. Mitochondrial DNA
8. Subunits of ATP-sensitive potassium channel
9. Proinsulin or insulin conversion

B. **Genetic defects in insulin action**

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipodystrophy syndromes

C. **Diseases of the exocrine pancreas**—Pancreatitis, Pancreatectomy, Neoplasia, Cystic Fibrosis, Hemochromatosis, Fibrocalculous Pancreatopathy, Mutations In carboxyl ester lipase

D.**Endocrinopathies**—Acromegaly, Cushing's Syndrome, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma, Aldosteronoma

E. **Drug- or chemical-induced**—Vacor, Pentamidine, Nicotinic Acid, Glucocorticoids, Thyroid Hormone, Diazoxide, -Adrenergic Agonists,

F**. Infections**—Congenital Rubella, Cytomegalovirus, Coxsackie Virus

G. **Uncommon forms of immune-mediated diabetes**—Stiff-Person -Syndrome, Anti-Insulin receptor antibodies

H. **Other genetic syndromes sometimes associated with diabetes**—

Down's Syndrome, Klinefelter's Syndrome, Turner's Syndrome, Wolfram's Syndrome, Friedreich's Ataxia, Huntington's Chorea, Laurence-Moon-Biedl Syndrome, Myotonic Dystrophy, Porphyria, Prader-Willi Syndrome

IV. **Gestational diabetes mellitus (GDM)**

(Adapted from the American Diabetes Association, 2007.)

Type 1 diabetes is a disease resulting in insulin deficiency. . Type 1 diabetes is prominent as a disease of childhood, reaching a peak incidence around the time of puberty, but can present at any age.

Clinical clues are:

- considerable weight loss,
- hyperglycaemia which fails to correct with diet and
- OHA treatment,
- the presence of strong or persistent ketonuria at diagnosis, and
- autoantibody tests indicating autoimmune disease.

The highest rates of type 1 diabetes in the world are seen in Finland and other Northern European countries, with the exception of the island of Sardinia, which for unknown reasons has the second highest rate in the world.

The incidence of type 1 diabetes appears to be increasing in most populations. In Europe the annual increase is of the order of 3-4%, and is most marked in children under the age of 5 years. A subtype of type 1diabetes (type 1B) has recently been described in Japanese patients

with an abrupt onset, no autoimmune disease and high serum pancreatic enzyme concentrations at diagnosis. This has not been described in other populations.

PATHOGENESIS OF TYPE-1 DIABETES MELLITUS

WHO (1995) estimated that there are 19.4 million people with type 1 diabetes and that the number will rise to 57.2 million by 2025.

The Diabetes Control and Complications Trial (DCCT-1995)[1] provided definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of type 1 DM.

This large multicenter clinical trial randomized over 1400 individuals with type 1 DM to either intensive or conventional diabetes management, and prospectively evaluated the development of retinopathy, nephropathy, and

neuropathy. Individuals in the intensive diabetes management group received multiple administrations of insulin each day along with extensive educational, psychological, and medical support.

Individuals in the intensive diabetes management group achieved a substantially lower hemoglobin A1C (7.3%) than individuals in the conventional diabetes management group (9.1%).The DCCT demonstrated that improvement of glycaemic control reduced non -proliferative and proliferative retinopathy (47% reduction), microalbuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycaemic control also slowed the progression of early diabetic complications.

Individuals in the intensive diabetes management group for a mean of 6.5 years had a 42–57% reduction in cardiovascular events [nonfatal myocardial infarction (MI), stroke, or death from a cardiovascular event] at a mean follow-up of 17 years, even though their subsequent

glycaemic control was the same as those in the conventional diabetes management group.

The benefits of an improvement in glycaemic control occurred over the entire range of HbA1C values suggesting that at any HbA1C level, an improvement in glycaemic control is beneficial. The goal of therapy is to

achieve an HbA1C level as close to normal as possible, without subjecting the patient to excessive risk of hypoglycemia.

The United Kingdom Prospective Diabetes Study (UKPDS[3]) studied the course of >5000 individuals with type 2 DM for >10 years. This study utilized multiple treatment regimens and monitored the effect of intensive glycaemic control and risk factor treatment on the development of diabetic complications. The (UKPDS[3]) demonstrated that each percentage point reduction in HbA1C was associated with a 35% reduction in micro vascular complications.

ASSESSMENT OF LONG-TERM GLYCEMIC CONTROL

Measurement of glycated hemoglobin is the standard method for assessing long-term glycemic control. When plasma glucose is consistently elevated, there is an increase in nonenzymatic glycation of hemoglobin; this alteration reflects the glycemic history over the previous 2–3 months, since erythrocytes have an average life span of 120 days (glycemic level in the preceding month contributes about 50% to the A1C value).

There are numerous laboratory methods for measuring the various forms of glycated hemoglobin, and these have significant interassay variations. Since glycated hemoglobin measurements are usually compared to prior measurements, it is essential for the assay results to be comparable. Depending on the assay methodology, hemoglobinopathies, anemias, reticulocytosis, transfusions, and uremia may interfere with the A1C result. Measurement of A1C at the "point of

care" allows for more rapid feedback and may therefore assist in adjustment of therapy.

Glycated hemoglobin or A1C should be measured in all individuals with DM during their initial evaluation and as part of their diabetes care.

As the primary predictor of long-term complications of DM, the A1C should mirror, to a certain extent, the short-term measurements of SMBG. These two measurements are complementary in that recent intercurrent illnesses may impact the SMBG measurements but not the A1C. Likewise, postprandial and nocturnal hyperglycemia may not be detected by the SMBG of fasting and preprandial capillary plasma glucose but will be reflected in the A1C.

In standardized assays, the A1C approximates the following mean plasma glucose values:

an A1C of 6% is 7.5 mmol/L (135 mg/dL),

7% is 9.5 mmol/L (170 mg/dL),

8% is 11.5 mmol/L (205 mg/dL), etc.

[A 1% rise in the A1C translates into a 2.0-mmol/L (35 mg/dL) increase in the mean glucose.]

In patients achieving their glycemic goal, the ADA recommends measurement of the A1C at least twice per year.

More frequent testing (every 3 months) is warranted when glycemic control is inadequate, when therapy has changed, or in most patients with type 1 DM. The degree of glycation of other proteins, such as albumin, can be used as an alternative indicator of glycemic control when the A1C is inaccurate (hemolytic anemia, hemoglobinopathies).

The fructosamine assay (measuring glycated albumin) reflects the glycemic status over the prior 2 weeks. Alternative assays of glycemic control (including the 1,5 anhydroglucitol assay) should not be routinely used since studies demonstrating that it accurately predicts the complications of DM are lacking.

CARDIOVASCULAR MORBIDITY AND MORTALITY

Cardiovascular disease is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in PAD, CHF, CAD, MI, and sudden death (risk increase from one- to fivefold) in DM.

The American Heart Association has designated DM as a major risk factor for cardiovascular disease (same category as smoking, hypertension, and hyperlipidemia). The absence of chest pain ("silent ischemia") is common in individuals with diabetes, and a thorough cardiac evaluation is indicated in individuals undergoing major surgical procedures.

The prognosis for individuals with diabetes who have CAD or MI is worse than for non diabetics. CAD is more likely to involve multiple vessels in individuals with DM.

In addition to CAD, cerebro vascular disease is increased in individuals with DM (threefold increase in stroke). Individuals with DM have an increased incidence of CHF.

The etiology of this abnormality is probably multi factorial and includes factors such as myocardial ischemia from atherosclerosis, hypertension, and myocardial cell dysfunction secondary to chronic hyperglycemia.

THE MECHANISM RESPONSIBLE FOR THE DEVELOPMENT OF HEART FAILURE IN DIABETES.

Risk factors for CHF are common in patients with Diabetes

Direct effect of diabetes on the myocardium.

Diabetes may activate the neuro hormonal system.

EFFECTS OF DIABETES ON THE MYOCARDIUM

Both systolic and diastolic abnormalities have been demonstrated in patients with Diabetes without symptomatic evidence of cardiovascular disease. These abnormalities correlate with duration of diabetes and evidence of retinopathy/neuropathy (Annonu et.al 2001) [21].

ADVANCED GLYCOSYLATION END PRODUCTS (AGEs)-

in hyperglycaemia , glucose reacts non enzymaticaly with proteins producing AGEs (Jyothirmayi et al., 1998)[33].The AGEs are thought to be involved in a number of detrimental biochemical processes

REACTIVE OXIDATIVE SPECIES –

Prolonged hyperglycaemia causes increased oxidative stress and leads to increase in apoptosis in failing human heart (Frustaci et al., 2000) [28]

(SERCA 2a)

Sarcoplasmic / endoplasmic reticulum Ca2+-ATPase 2a SERCA2a replenishes intracellular calcium stores and is thought to play a important role in cardiac relaxation. AGE s cause post translational modification of SERCA 2a and result decreased in activity

PROTEIN KINASE C –

Increased activation of the signal transduction pathway for protein kinase C (Way et al 2001[38]), elevated levels of protein kinase C activity is found in failing heart (bowling et al., 1999[28]). Over expression of protein kinase c activity leads to myocardial hypertrophy and

dysfunction .Elevation of protein kinase C activity is found in response to hyperglycaemia in cultured endothelium(way et al.,2001[38]).Increase protein kinase c activity leads to an increased in extra cellular matrix deposition causing thickening of basement membrane ,altered colour flow and increases vascular permeability ,(Zhang et.al 2003)

VASCULAR ENDOTHELIAL GROWTH FACTOR-(VEGF)-

VEGF is expressed in response to hypoxia and may play an important role in vascular injury. Following myocardial infarction VEGF m RNA is increased in arteriolar smooth muscle cells and infiltrating macrophages around infarct size.(shinohara et al 1996) [36].In diabetes there is a reduction in the amount of VEGF and its receptor found in the myocardium in comparison to patients without diabetes.(chou et al ., 2002) [27].This is consistent with pathological report of decreased collateralisation in diabetic myocardium following ischemia.(Abaci et al.,1999) [40]

In the myocardium, prolonged hyperglycaemia has shown the increase gene expression of muscle carnitine palmitoyl transferase-1(zhang et al., 2002) [39].

This is a mitochondrial enzyme involved in the transportation of FFA s into the mitochondria, promoting the myocardial use of FFAs.

PATHOLOGICAL EFFECTS IN THE HEART AND THE BLOOD VESSELS

ENDMYOCARDIAL DYSFUNCTION

Endmyocardial dysfunction is a feature of both diabetes and CHF. In patients with diabetes and insulin resistant individual endothelial function is grossly impaired (steinbreg et al .,1999) [37]. Hyper glycaemic has been shown to impair production of endothelium derived Nitric oxide (tesfamarian et al ., 1991) [41] .

Hyperglycaemia also stimulates extra cellular matrix production , thickening of the basement membrane in cultured endothelial cells (cagliero et al 1991) [42].

Both hyperglycaemia have shown to increase production of reactive oxygen species by culture endothelial cells (Inoguchi et al -, 2000) [43]. The AGE s is involved in the deactivation of nitric oxide and they impair vaso dilation.

ARTERIAL STIFFNESS

Diabetes increases arterial stiffness in humans. Pulse pressure is a marker of arteriolar stiffness and predicts cardiovascular risk in patients with diabetes. Stiff arteries alter the haemodyanamics state in such a way that after load is increased and coronary perfusion pressure is decreased. It had been suggested that resultant myocardial ischemia, if chronic, could lead to myocardial fibrosis and impaired systolic function.

CARDIAC AUTONOMIC NEUROPATHY

Patients with autonomic neuropathy have an impaired coronary vasodilator response to sympathetic stimulation .Diabetic micro angiopathic vascular disease has been suggested as a potential contributor to myocardial dysfunction in patients with diabetes.

LEFT VENTRICULAR FUNCTION IN DIABETES MELLITUS

Since the original description by Rubler et al based on their study from four adult diabetic subjects with non coronary cardiac failure and subsequent observation by the Framingham workers about the most frequent occurrence of CCF among the diabetics than could explained by the hypertension or ischemic heart disease alone.

Pathological evidence among the nine diabetic subjects without significant atherosclerosis on post mortem examination by Regan et al about the presence of Periodic Acid Schiff positive material, presumably

a glyco protein the interstitium of the myocardium lent further support to existence of a specific type of heart muscle disease among diabetics.

Since the original description by Rubler et al based on their study from four adult diabetic subjects with non-coronary congestive cardiac failure (CCF) and subsequent observations by the Framingham workers about the most frequent occurrence of CCF among the diabetics than could be explained by hypertension or ischemic heart disease alone, interest was renewed in the field of cardiac involvement in long-standing diabetic patients.

Impaired left ventricular (LV) function may frequently be detected in asymptomatic diabetic subjects and is related to the extent of diabetes and evidence of micro vascular complications. Although systolic and diastolic functions of the heart are impaired in diabetes, many studies have shown that the LV diastolic abnormalities are most common and may in fact precede the development, of systolic abnormality.

EVALUATION OF LV FUNCTION IN DIABETIC SUBJECTS

There are two chief methods of evaluating the LV function

- Utilizing the non-invasive techniques.
- Invasive techniques

Non-invasive methods include the assessment by

a) Systolic time intervals (STI)

b) Apex cardio graphy (ACG)

c) Radio nucleotide ventriculography

d) Echocardiography and cardiac Doppler

Invasive method is by cardiac catheterization delineating the coronary artery anatomy and LV angiography. This procedure is usually reserved for symptomatic diabetic subjects with overt or those who manifest CCF and is unnecessary in asymptomatic although long-standing diabetics.

LV DIASTOLIC FUNCTION

It is now clear from the various studies that the primary functional abnormality in a diabetic heart is the impairment of LV diastolic function reflecting the reduced LV filling and that even the systolic functional alteration is the result of reduced LV filling.

Diastolic function can be detected by echocardiographic technique in a significant number of diabetics with longer duration of both Type 1 and 2 Diabetes mellitus patients with or without overt cardiac disease or other micro vascular complications.

M-MODE AND 2-D ECHOCARDIOGRAPHY

Aerakisnen et al utilizing the digitalized M-mode technique studied 36 female IDDM patients with a mean duration of diabetes of 10 years or more and found that the most common abnormality (19 pts) was prolonged rapid filling period while the systolic function was normal in all.

Another study recorded simultaneous echo and phonocardiogram in142 diabetics. The LV relaxation, the rate and duration of cavity dimension increase and wall thinning were determined. Delayed mitral valve opening (MVO) relative to minimal LV cavity dimension and aortic valve closure (AVC) was found in all but 12 subjects, especially in those with

micro vascular complications. Prolongation of isovolumic relaxation time (IVRT) i.e. measured as period between AVC and MVO (abnormal, if more than 110 m sec), which can be demonstrated using dual M-mode echo preferably at 100 min/sec speed showing simultaneous aortic and mitral valve levels, is an important diastolic abnormality, as found by Sanderson et al .

Others using quantitative cross-sectional echocardiography and stress myocardial perfusion scintigraphy found that diabetic subjects had mildly reduced LV end diastolic volumes and impaired diastolic filling as assessed by lower left atrial emptying index compared to controls .The left atrial emptying index is defined on M-mode tracing of the aorta.

DOPPLER TECHNIQUES

Pulsed Doppler ultrasound interrogation of mitral inflow velocities (Doppler cursor placed at the tips of the mitral leaflets on apical 4-chamber view) gives a simple and reproducible method of determining the LV filling that correlates well with radio nucleotide and invasive techniques.

Ventricular filling in the normal subjects is characterized by a biphasic pattern with an initial peak velocity of rapid early ventricular filling ('E') and a relatively low peak velocity of late inflow due to atrial contraction (A).

Impaired diastolic filling of the left ventricle in both Type 1 and Type 2 asymptomatic diabetics without the evidence of cardiovascular

disease and unrelated to microangiopathic complications has been demonstrated using PW Doppler which showed reduction in the early filling velocity (reduced 'E' peak) and compensatory increase in the late flow (increased 'A' peak) and thus increased A/ E ratio

(i.e. A/E more than 1).

Besides, the deceleration of 'E' velocity is prolonged indicating a slow rapid-filling phase ('E' deceleration more than 250 m/sec). Increased atrial contribution to LV filling can be assessed by the area under the late diastolic filling envelope compared to the total diastolic area. Various studies have demonstrated these above Doppler findings in young diabetic subjects without evidence of heart failure.

A 3-year follow-up study by Charella et al of a group of asymptomatic diabetics with slow filling and wall thinning demonstrable on echocardiography showed 31% developing heart failure and 19% that died.

Measurement of LV diastolic function may therefore prove to be a

useful indicator of cardiovascular morbidity and mortality in diabetics.

Hence,

Abnormal diastolic function suggestive of reduced LV compliance resulting in a 'Stiff' myocardium appears to be the hall mark of the specific type of diabetic heart muscle disease. The presence or addition of hypertension or coronary artery disease will certainly put a new burden on the already 'non-compliant' myocardium in long-standing diabetics with or with out micro vascular complications.

PROGNOSIS

The prognosis of left ventricular dysfunction is influenced by

1) Degree of glycaemic control
2) Extent of ventricular fibrosis and diffuse ischemia

Tight glycaemic control relatively delays the dysfunction as the damage by the ischemia is irreversible and it relatively carries a

good prognosis. Further studies are required to determine whether the other agents are able to influence the myocardial function.

TREATMENT

It is unlikely that the drugs and dietary measures are less likely influence the development of the microangiopathy. Coronary artery has no role in LV dysfunction in the absence of angina due to CAD.

Two methods are currently available to modify the micro angiopathy

1) Tight control of blood sugar levels by continuous subcutaneous insulin infusion (CSI) has been shown to halt or occasionally revert the microangiopathy.

2) Alteration of haemorrheology with Aspirin, Dipyridamole, Ticlopedine, & Sulphinpyrosone may influence micro angiopathy.

But that the effect of tight control of blood sugar may improve the LV function is still not proven, it could delay the progress of LV dysfunction.

With the aforesaid introduction of Diabetic Cardiomyopathy our study results are comparable with that of previous authors.

MATERIALS AND METHODS

MATERIALS AND METHODS

The Clinical materials were of Type-1 Diabetes Mellitus individuals selected from Diabetic out patient department in the AGM government hospital,Trichirappalli .

About 87 patients were subjected to initial assessment it included through clinical examination, routine blood investigation consisting of complete blood count, biochemistry investigation, ECG , estimation of HbA1c and echo cardiography were done from which 50 patients were included in the study.

Patients with following criteria are excluded from the study

- Patients with abnormal resting ECG suggestive of ischemic heart disease or bundle branch block etc.
- Presence of co morbid disease known to influence Left ventricular dysfunction:- Thyroid disease, Alcoholism and Hypertension.
- Evidence of heart disease and clinical heart disease patient,
- Peripheral vascular disease,
- Cigarette smoking.
- Dyslipidemia

Only patients who were in sinus rhythm, free from signs and symptoms congestive cardiac failure, Hypertension, Anemia, Ischemic heart disease were included for this study.

Place of study:

ANNAL GANDHI MEMORIAL GOVERNMENT HOSPITAL, TIRUCHIRAPPALLI

K.A.P.V.GOVERMENT MEDICAL COLLEGE, TIRUCHIRAPPALLI

Total number of patients – 50(Selected from the list of 87)

They were divided into two groups according to the Glycaemic status one group consisted of HbA1C levels < 7, and

the other group consisted of HbA1C levels > 7.

The number patients included in to each group was 25.

All of them were subjected to echo cardiography done at the Department of Cardiology, AGMGH, Tiruchirappalli.

Echocardiography was performed in the post absorptive phase.

ALOKA 830 equipment which has the capabilities of performing two dimensional, M mode, Pulsed wave and continuous wave Doppler and colour flow imaging was used to obtain echo cardiogram images.

Phased array transducers 2.5 - 3.5 MHz frequencies were used to obtain 2-D / M-mode echo cardiography. Images were obtained with subjects in 30 degree lateral decubitus position. All measurements were performed in the freezed images from all the patients, good quality images suitable for the measurements and interpretations were obtained and recorded.

For assessment of LV systolic function the following parameters were calculated from the M- mode echocardiogram obtained at the level of mitral valve chordae.

LV dimension (minor axis) diastole (LVId) systole (LVsd) and thickness of inter ventricular septum, left ventricular posterior wall thickness in diastole.

LV ejection fraction was calculated using the following formula,

EF= LVEDV-LDESV/ LVEDV x 100

Specific attention was focused on diastolic function namely

1. Calculation of left ventricular inflow velocities(e),
2. Peak atrial contraction in Systole(a)
3. Calculation of a/e ratio and
4. Deceleration time
5. Iso volumic relaxation time.

DATA ANALYSIS

The mean and standard deviation of the all the parameters was analyzed using following formula.

INDEPENDENT T – TEST

Formula $\frac{x1 - x2}{s2(1/n1+1/n2)}$

x1 – mean of sample -1

x2 _ mean of sample -2

n1 – Number of subjects in sample-1

n2 – Number of subjects in sample-2

$$x12\text{-}x12/n1 + x22\text{-}x2/n1$$

n1+n2 -2

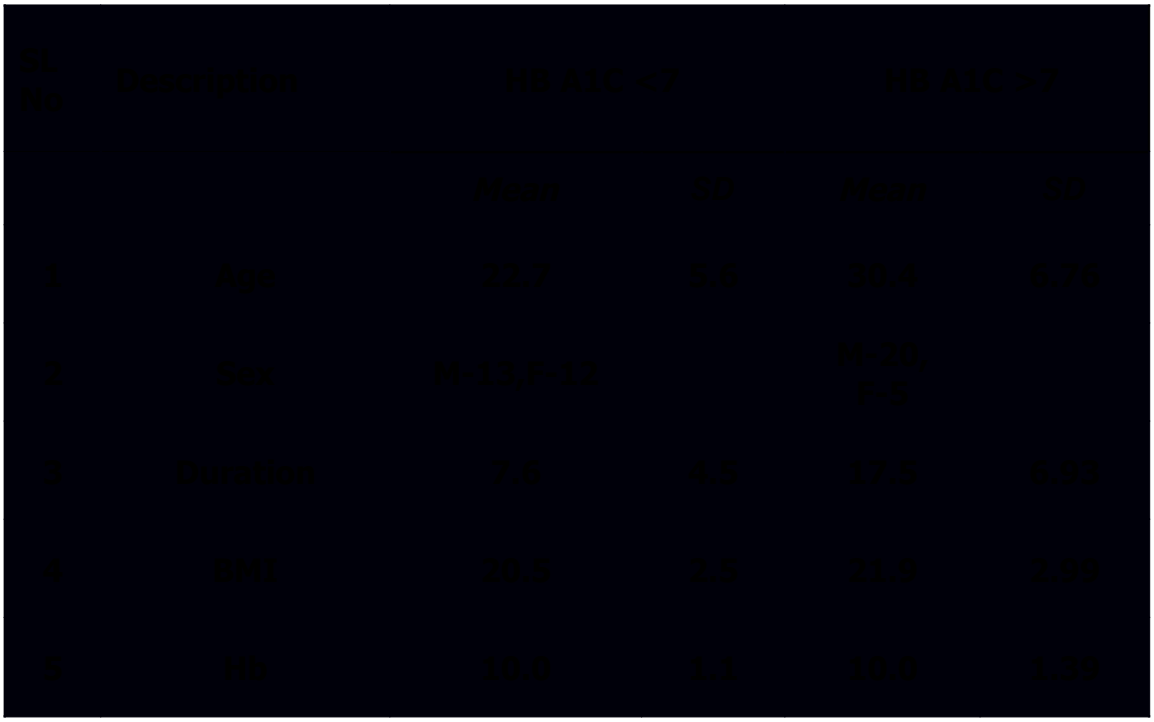
The patients divided into two groups according to their HbA1c level as taking cutoff value as 7. The echo parameter of the two groups are analysed using the independent t-test and the P-value got from the t-test table.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

The Basic characteristic of two groups well and poorly controlled Type 1 diabetes mellitus.

Table No 1.



6	Urea	25.6	4.6	21.2	6.29
7	S.creatinine	0.6	0.2	0.7	0.2
8	HBA1C	5.88	0.698	8.73	0.9

DISCUSSION

DISCUSSION

In this study, we found a higher prevalence of asymptomatic diastolic dysfunction in type 1 diabetes mellitus, in the absence of hypertension and cardiac disease.

These results support the concept of a specific **Subclinical Diabetic Cardiomyopathy,** which may be related to glycaemic control.

It showed that children and adolescents with type 1diabetes had altered cardiac function compared with age-matched individuals without diabetes.

Subjects included in the study had no cardiac signs or symptoms or diabetes complications, and were not taking medications known to modify cardiac structure or function.

The most striking findings were recorded in patients with type 1 diabetes, who had reduced diastolic function compared with control subjects.

Prolonged isovolumic relaxation time reflects the rate of active left ventricular diastolic relaxation between aortic valve closure and opening of the mitral valve. Relaxation of the myocardium is an energy

dependent process requiring calcium sequestration from the cytosol into the sarcoplasmic reticulum, and it is altered in diabetes.

Interestingly, recent magnetic resonance studies have correlated changes in myocardial high-energy phosphates and parameters of diastolic function in patients with type 2 diabetes.

Experimental studies have also shown abnormalities in the calcium pump activity in diabetic animals (diamante et al (2003)[11].

In this study, we found high Trans mitral A/E ratio as an evidence of reduced diastolic function, left ventricular chamber compliance, and changes in the left atrial pressure. In the presence of mild diastolic dysfunction, early filling is often reduced, leading to an exaggerated atrial contribution to left ventricular filling and a high A/E ratio.

In more advanced heart failure, this pattern is often lost due to high left atrial and left ventricular pressure and the A/E ratio pseudo-normalizes or increases, complicating interpretation (Garcia et al (1998) [6].

Prior studies have shown a correlation between HbA1c and diastolic function in older individuals with type 1 diabetes, suggesting that glycaemic control maybe an important determinant of diastolic function - Shishehbor (2003)[(12).]

Hyperglycemia influences heart metabolism, the production of advanced glycosylation end products, oxidative stress, and protein kinase C activation -Young et al (2003)[13], young et al (2005)[14] .

The relation between glycaemic control and diastolic indexes in study supports the hypothesis that hyperglycemia by itself can lead to Subclinical Cardiomyopathy.

Results indicate that diabetic patients with worse glycaemic control are at an increased risk of early diastolic dysfunction.

Therefore, in our study, patients with type 1 diabetes had increased isovolumic relaxation time, and a increased A/E ratio compared with normal volunteers.

These results are consistent with prior studies in asymptomatic normotensive type 1 and 2 diabetic patients (Young LH (2004)[14], Zabalgoitia M (2001)[15] , Liu JE(2001)[16]; Shivalkar (2005) [17] Grand (2006)[18]

Also, diastolic dysfunction was closely related to the duration of diabetes.

Further study is needed to determine whether

- Intensification of glycaemic control improves diastolic parameters

- Drugs that could interfere cellular level in cardiac metabolism
- Is diastolic dysfunction reversible ,if so, the time limit

SUMMARY

SUMMARY

Left ventricular diastolic dysfunction is a core feature of diabetic heart disease.

The aim of this prospective study was to evaluate the relation of hemoglobin A1c and diastolic function in type 1diabetes mellitus.we examined echocardiographic studies of 25 patients with type 1 diabetes without clinical evidence of heart disease and hemoglobin A1C<7 and 25 patients with type 1 diabetes without clinical evidence of heart disease and hemoglobin A1C>7 .

In patients with type 1 diabetes without clinical evidence of heart disease and HbA1c >7, ***there was a diastolic dysfunction with higher trans mitral A/E ratio (0.6±0.1 vs 0.9±0.19 p<0.001), more prolonged isovolumic relaxation time (68±7.3 vs 84±)*** *in comparison with patients with type 1 diabetes without clinical evidence of heart disease and hemoglobin A1C<7 subjects.*

Furthermore, HbA1c correlated with diastolic Doppler indices.

These results demonstrate that

1. *Asymptomatic diastolic dysfunction is common in patients with type 1 diabetes mellitus and can be picked up early before the clinical manifestation,*
2. *Severity of the diastolic dysfunction correlates with the glycaemic control,*
3. *Theoretical reversibility of these early cardiac changes with drugs can prevent progress in the clinical heart failure.*

EVALUATION OF DIASTOLIC DYSFUNCTION IN ASYMPTAMATIC

TYPE-1 DIABETIC PATIENTS AND CORRELATES WITH HBA1C LEVELS.

NAME AGE SEX

REG NO ADDRESS

TYPE OF DIABETES- TYPE-1

DURATION

INJ INSULIN

INJ INSULIN +OAD

OTHER CO MORBID CONDITION

HYPER TENSION TB ASTHMA OTHERS

PERSONAL HISTORY

DIET ADDICTION

SMOKER ALCOHOLISM

FAMILY HISTORY

HYPER TENSION DM CAD COPD

AFFECTED PERSON

FATHER MOTHER SISTER BROTHER

OTHERS

CLINICAL EXAMINATION

HEIGHT WEIGHT BMI

GENERAL EXAMINATION PR BP

SYSTEMIC EXAMINATION

CVS

RS

P/A

CNS

INVESTIGATIONS

CBC

RBC

WBC

P- L- M- E-

PLATELETS

PCV

HB

BLOOD SUGAR

FASTING

2HR PP

HBA1C

B.UREA

S.CREATININE

URINE ROUTINE

ALBUMIN SUGAR DEPOSITS

ECHO

BASELINE ECHO CHARACTERS

1) LEFT ATRIAL AREA(cm2)
2) LV MASS INDEX (gm2)
3) LV EJECTION FRACTION(%)
4) POSTERIOR LV DIAMETER(cm)
5) IVS WALL THICKNESS
6) LV END DIASTOLIC DIAMETER

DOPPLER INDICES

1) LV PEAK EJECTION TRANS MITRAL FLOW VELOCITY-(E)-cm/s
2) PEAK ATRIAL CONTRACTION-(A)-cm/s
3) E/A- RATIO
4) DECELERATION TIME
5) ISO VOLUMIC RE3LAXATION TIME(ms)

BIBILIOGRAPHY

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1. The diabetes control and complication trial research group; Diabetes 44:968 ,1995
2. American diabetes association clinical practice &recommendation 2007.Diabets care 30:s4 2007
3. United kingdom prospective Diabetes study (UKPDS) group 1998, intensive blood sugar control with insulin or sulfonylureas with conventional treatment and risk of complication in type- 2 DM.
4. Diastolic dysfunction is associated with altered myocardial metabolism in asymptomatic normotensive patients with well-controlled type 2 diabetes mellitus. J Am Coll Cardiol 2003;42:328-335.
5. Eisenberth GS update in type 1 Diabetes J clin Endocrinology metabolism 2;2403,2007
6. Natan et al intensive diabetes treatment and cardio vascular disease in patient with type 1 N Eng J Med353;2643
7. Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the studastolic function. J Am Coll Cardiol 1998;32:865- 875 Zile MR, Baicu CF, Gaasch WH.
8. Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953-1959.
9. Boyer JK, Thanigaraj S, Schechtman KB, Perez JE.Prevalence of ventricular diastolic dysfunction in

asymptomatic, normotensive patients with diabetes mellitus. Am J Cardiol 2004;93:870-875.

10.

11. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-458.
12. Garcia MJ, Ares MA, Asher C, Rodriguez L, Vandervoort P, Thomas JD. An index of early left ventricular filling that combined with pulsed Doppler peak E velocity may estimate capillary wedge pressure. J Am Coll Cardiol 1997;29:448-454.
13. Diamant M, Lamb HJ, Groeneveld Y, Endert EL, Smit JW, Bax JJ, Romijn JA, de Roos A, Radder JK.Diastolic dysfunction is associated with altered myocardial metabolism in asymptomatic normotensive patients with well-controlled type 2 diabetes mellitus. J Am Coll Cardiol 2003;42:328-335.
14. Shishehbor MH, Hoogwerf BJ, Schoenhagen P, Marso SP, Sun JP, Li J, Klein AL, Thomas JD, GarciaJ. Relation of hemoglobin A1c to left ventricular relaxation in patients with type 1 diabetes mellitus and without overt heart disease. Am J Cardiol 2003;91:1514-1517.
15. Young ME, McNulty P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetes. Part II:Potential mechanisms. Circulation 2002;105:1861-1870.
16. Young LH. Diastolic function and type 1 diabetes. Diabetes Care 2004;27:2081-2083.

17. Zabalgoitia M, Ismaeil MF, Anderson L, Maklady FA. Prevalence of diastolic dysfunction in normo tensive, asymptomatic patients with well controlled type 2 diabetes mellitus. Am J Cardiol 2001;87:320-323.

18.

19. Liu JE, Palmieri V, Roman MJ, Bella JN, Fabsitz R, Howard BV, Welty TK, Lee ET, Devereux RB. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. J Am Coll Cardiol 2001;37:1943-1949.

20. Shivalkar B, Dhondt D, Goovaerts I, Van Gaal L, Bartunek J, Van Crombrugge P, Vrints C. Flow mediated dilatation and cardiac function in type 1 diabetes mellitus. Am J Cardiol 2006;97:77-82. Epub 2005 Nov 16.

21. Grandi AM, Piantanida E, Franzetti I, Bernasconi M,Maresca A, Marnini P, Guasti L, Venco A. Effect of glycemic control on left ventricular diastolic function in type 1 diabetes mellitus. Am J Cardiol 2006;97:71-76. Epub 2005 Nov 14. Diabetologia Croatica 35-2, 2006 43.

22. Bueger AJ, Delia J, Weinrauch LA, Yeon SB, Aepfellbacher FC. Improved glycemic control induces regression of left ventricular mass in patients with type 1 diabetes mellitus. Int J Cardiol 2004;94:47-51.

23. Annou Ak et al, left ventricular systolic and diastolic functional abnormalities in asymptomatic patients with non

insulin dependent diabetes mellitus . journal of the American society of echo cardiography 14 :885-91

24. Baski Cj, et al, comparison of up titration of gliclazide with the addition of rosiglitazone to gliglazide patients with type 2 diabetes inadequately controlled on the half maximal dose Acta DIabetologica 41 :63-9
25. Bidasse KR et al, (2004) Diabetes increase the formation of advanced glycosylation end products on sarco plasmic reticulum Ca 2+ ATPase .Diabetes 53;463-73
26.
27. Bojunga J. et al .anti oxidative treatment prevent activation of death receptor and mitochondrion dependant apotosis in the heart of diabetic rats. Diabetolgica.
28. Bowling N et al increase protein kinase C activity and expression of calcium – sensitive is forms in the failing human heart . circulation 99 : 384-91
29. Chandler MP et al partial inhibition of fatty acid increase the regional contractile power and efficiency during demand induced ischaemia. cardi vascular research 59 ;143-51
30. Chou et al decreased cardiac expression of vascular endothelial growth factor and its receptor in insulin resistant and diabetes states ; a possible explanation for impaired collateral formation in cardiac tissue. Circulation 105:373-9
31. Fructasi et al myocardial cell death in human diabetes . circulation research 87:11232-32
32. Gupta et al increased plasma free fatty acid concentration and their significance in patients with acute myocardial infarction

33. Henderson et al, decreased contractility of rat heart muscle by free fatty acid during hypo glycaemic
34. Holmang et al, the effects of hyper insulinemia inon myocardial mass blood pressure regulation and central haemo dynamics in rats . europien journal of clinical investigation 26 :973-8
35. jyorthirmayi et al effects of metformin on collgen glycosylation and diastolic dysfunction in diabetic ocardium. journal of circulation pharmacology and therapeutics 3 : 319-26
36.
37. azegi et al down relation of myocardial enhancer factor 2 C and ocyte enhancer factor 2 c regulate gene expression in diabetic patients with non ischemic heart failure. circulation 106:407 -11
38. Rosen P et al role oxygen derived free radicals for vascular dysfunction in the diabetic rats prevention of alpha tocopherol ? molecular and cellular biochemistry 188:103-11
39. Sam et al increased reactive oxygen species production and functional alteration in antioxidant enzymes in the human failing g ocardium. Journal of cardiac failure .11:473-89
40. Shinhora K et,al expression of vascular endothelial growth factor in human myocardial infarction heart vessels 11 : 113-22
41. Stein berg et al obesity insulin resistance is associate with endothelial dysfunction . implication for the syndrome of insulin resistance .journal of clinical investigation 97-2058-64

42. Way et al (2001) Protein kinase C and the development of diabetic vascular complications, Diabetic Medicine 18:945-59
43. Zhang et al (2003) ,Protein Kinase C activation induces Angiotensin converting enzyme expression in neonatal rat cardiomyocytes, Cardiovascular research 57 :139-46.
44. Abaci et al (1999) effect of Diabetes Mellitus on the formation of coronary collaterals, Circulation 99 :2239-42
45. Tesfamariam et al (1991) Elevated glucose impairs endothelium dependant relxation by activating protein kinase C, journal of clinical investigations 87:1643-8
46.
47. Cageliero et al (1991) characteristic and mechanisms of high glucose induced over expression of basement membrane components in cultured human endothelial cells. Diabetes 40:102-10
48. Inoguchi et al (2000), high glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C dependant activation of NADH oxidase in cultured vascular cells.
49. Rubler et al(1972) new tyoe of cardiomyoprthy associated with diabetic glomeruloscelerosis American journal of cardiology 30:595-602.